

Association of Anemia Severity and Lactate Dehydrogenase With Clinical Complications in Adults With Sickle Cell Disease: A Panamanian Cohort

Niko Diaz García

nikodz04@gmail.com

Hospital Santo Tomas <https://orcid.org/0009-0008-5618-030X>

María Mantilla

Universidad Interamericana de Panama

Fernando Carrillo

Ciudad de la Salud

Lorena Ordoñez

Hospital Santo Tomas

Germán Espino

Hospital Santo Tomas

Research Article

Keywords: Sickle Cell, Lactate Dehydrogenases, Acute Chest Syndrome, Stroke, Leg Ulcer, Osteonecrosis

Posted Date: July 6th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9635916/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Sickle cell disease (SCD) is characterized by chronic anemia and vaso-occlusion leading to organ damage. The relative contribution of anemia severity and hemolysis to specific complications remains unclear, particularly in underrepresented populations. We conducted a retrospective cross-sectional study of 180 adults with SCD in Panama. Hemoglobin and lactate dehydrogenase (LDH) were categorized into quartiles. Multivariable logistic regression assessed associations with acute chest syndrome, stroke, leg ulcers, and avascular necrosis, adjusting for age, sex, and hydroxyurea use. Lower hemoglobin levels were associated with reduced risk of avascular necrosis in the overall cohort (OR 0.12; 95% CI, 0.03–0.62; $p = 0.011$) and in the HbSS subgroup (OR 0.14; 95% CI, 0.03–0.72; $p = 0.019$). Higher LDH levels were associated with increased risk of acute chest syndrome (OR 1.37; $p = 0.033$) and avascular necrosis in HbSS (OR 2.68; $p = 0.044$). No significant associations were found for stroke or leg ulcers. These findings suggest overlapping roles of anemia and hemolysis in SCD complications.

INTRODUCTION

Sickle cell disease (SCD) is one of the most common genetic disorders worldwide (1) and represents a major public health concern, particularly in low- and middle-income countries. It is estimated that more than 300,000 children are born with SCD each year, with projections exceeding 400,000 annual cases by 2050, reflecting its growing global burden (2, 3).

From a pathophysiological standpoint, SCD results from a β -globin mutation that produces hemoglobin S, which polymerizes under deoxygenated conditions, leading to erythrocyte deformation. This process drives two central mechanisms: chronic hemolysis and vaso-occlusion, both of which contribute to progressive organ damage and most clinical manifestations (3, 4).

Clinically, SCD is highly heterogeneous. Some patients develop predominantly vaso-occlusive complications, such as pain crises and avascular necrosis, whereas others exhibit manifestations more closely related to hemolysis, including endothelial dysfunction and vascular complications. This variability has led to the proposal of distinct pathophysiological sub phenotypes, broadly categorized as hemolysis-driven or viscosity-driven (5, 6). These mechanisms suggest that hemolysis and hemoglobin concentration represent distinct but interrelated pathways in the development of clinical complications.

In this context, laboratory parameters such as hemoglobin and lactate dehydrogenase (LDH) have gained relevance as indirect markers of these processes. LDH has been widely used as a marker of intravascular hemolysis and has been associated with increased disease severity and vascular complications. Recent studies have reinforced its role in clinical risk stratification in SCD (7–9). Among available biomarkers, hemoglobin and LDH are readily accessible in routine clinical practice, making them especially relevant for risk stratification across diverse healthcare settings.

Hemoglobin levels not only reflect anemia severity but also influence blood viscosity. Relatively higher hemoglobin levels may promote vaso-occlusion by increasing microvascular flow resistance, potentially

contributing to complications such as avascular necrosis (5, 10).

Despite these advances, the independent and combined contributions of hemolysis and anemia severity to specific clinical complications remain incompletely defined, and findings have been inconsistent across populations. Furthermore, data from Latin America, particularly in adult populations, are limited, restricting the generalizability of existing evidence and the understanding of disease expression in these settings (11, 12).

This gap limits accurate risk stratification and the optimization of therapeutic strategies. In addition, variability across populations suggests that socioeconomic factors, access to care, and genetic background may influence disease phenotype and outcomes (2, 13).

To address these gaps, we conducted a cohort study of adult patients with SCD in Panama, a population characterized by a high burden of chronic complications.

The objective of this study was to evaluate the association between anemia severity and hemolysis, measured by hemoglobin and LDH levels, and the development of vascular complications in adults with SCD. We hypothesized that higher LDH levels and lower hemoglobin concentrations are associated with an increased risk of clinical complications.

MATERIALS AND METHODS

Study design

We conduct an observational, analytical, retrospective, cross-sectional study to assess the association between anemia severity and LDH levels with vascular complications in adults with sickle cell disease, done between January 2023 and December 2024, at the hematology outpatient clinic of Santo Tomás Hospital. Adult patients aged ≥ 18 years with confirmed sickle cell disease (HbSS, HbSC, or HbS β^+) were eligible for inclusion and identified through institutional clinical registries. Exclusion criteria included incomplete clinical, laboratory data required for the analysis and patients with other hematologic conditions that could affect hemolysis markers or hemoglobin levels.

Data collection

Data were obtained from clinical records and laboratory databases. Complications and treatment use were recorded based on physician documentation and laboratory data. All measurements were performed within the same healthcare system, ensuring comparability across patient groups, hemoglobin, LDH, bilirubin, reticulocyte count, and other laboratory parameters were measured as part of routine clinical care using standardized hospital laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease–Epidemiology Collaboration formula (CKD-

EPI) 2021 (14). The number of transfusions, hospitalizations, and vaso-occlusive crises were defined as the total number of events occurring within the 12 months preceding each patient's inclusion date.

The primary outcomes were sickle cell disease–related vascular complications, including acute chest syndrome, stroke, leg ulcer, and avascular necrosis. Outcomes were defined according to documented clinical diagnoses in the medical records. Selection bias was minimized by including all eligible patients meeting predefined criteria within the study period. Information bias was reduced by standardized clinical and laboratory records. Residual confounding cannot be excluded given the observational nature of the study. Race and ethnicity were recorded from clinical records as reported in institutional registries. No sample was calculated, as this was a retrospective study including all eligible patients within the study period.

Statistical approach

The characteristics of the three phenotypic groups (HbSS, HbSC, and HbSβ⁺) were compared using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were compared using the Kruskal–Wallis test, while Associations between hemolysis biomarkers and clinical outcomes were evaluated using logistic regression models, reporting odds ratios (ORs) with 95% confidence interval (CI). Anemia severity was assessed using hemoglobin levels and categorized into; quartile 1 versus quartiles 2–4. LDH was used as a marker of hemolysis and categorized as high versus low based on the upper quartile (quartile 4 vs quartiles 1–3). Multivariable models were adjusted for age and sex, with additional adjustment for hydroxyurea use in the hemoglobin model. The associations were assessed in the whole population and in the SS phenotypic group. Analyses were performed using available-case analysis. Missing data were reported where relevant. The analysis was made using Jeffreys's Amazing Statistics Program (JASP) version 0.96, graphical visualizations, including forest plots, were produced in R version 4.5.3. A 2-sided P value < 0.05 was significant.

Ethical considerations

The study was registered in the Clinical Research Registry System of the Ministry of Health of Panama (RESEGIS) under code 4875 and was approved by the Institutional Research Ethics Board of Hospital del Niño Dr. José Renán Esquivel under code 202601-0009. Given the retrospective design the requirement for informed consent was waived.

RESULTS

Population description

A total of 220 adult patients with sickle cell disease (SCD) treated at the hematology outpatient clinic of Santo Tomás Hospital in Panama met the eligibility criteria for our study. Twenty of these patients were

excluded: 10 due to incomplete clinical data, 13 due to missing laboratory results, and 2 due to the presence of other hematologic malignancies. Therefore, our study cohort consisted of 180 adult patients with SC. These patients were classified according to their SC phenotypes as follows: 156 patients with HbSS (86.7%), 21 with HbSC (11.7%), and 3 with HbSβ+ (1.7%). (Fig. 1)

SCD, Sickle cell disease; HbSS, Hemoglobin SS; HbSC, Sickle Hemoglobin C Disease; HBSB+, Sickle Beta-Plus Thalassemia.

Baseline characteristics

Baseline demographic characteristics were similar across phenotypes, with no significant differences in sex ($p = 0.522$), age (median [IQR]: HbSS 28 [22–40], HbSC 26 [18–46], HbSβ+ 20 [18–22.5]; $p = 0.273$), geographic origin, or race.

Hematological parameters and markers of hemolysis showed significant differences between the groups: patients with HbSS had significantly lower hemoglobin levels: median (IQR) 7.8 (7.0–8.9) g/dL vs. 11.2 (11.0–12.2) g/dL for HbSC and 12.2 (12.2–12.6) g/dL for HbSβ+; ($p < .001$) and hematocrit: median (IQR) 22.6 (19.9–25.4) % vs. 30.7 (24.2–31.9) % for HbSC and 35.5 (34.7–35.8) % for HbSβ+; ($p < .001$). In contrast, HbSS patients had the highest levels of hemolysis markers, including reticulocytes: median (IQR) 11.8% (8.4–17.0) vs. 4.9% (4.3–8.0) for HbSC and 6.5% (6.1–6.9) for HbSβ+; $p = 0.003$, total bilirubin: median (IQR) 3.0 (2.1–4.9) mg/dL vs. 2.1 (1.7–2.8) mg/dL for HbSC and 1.1 (1.0–1.2) mg/dL for HbSβ+; ($p = 0.007$) and LDH: median (IQR) 695 (421–911) U/L vs. 422 (230–455) U/L for HbSC and 208 (196–217) U/L for HbSβ+; ($p < .001$). (Fig. 2)

Panels show haemoglobin (A), hematocrit (B), mean corpuscular volume (MCV) (C), reticulocyte percentage (D), total bilirubin (E), and lactate dehydrogenase (LDH) (F) according to phenotype (HbSS, HbSC, and HbSβ+). Data are presented as boxplots with individual observations. Comparisons between groups were performed using the Kruskal–Wallis test.

The remaining laboratory parameters, such as ferritin, creatinine, and eGFR, did not show statistically significant differences between the phenotypes. Among the treatment variables, the use of hydroxyurea showed statistically significant differences, being more common in patients with HbSS ($N = 118$; 75.6%) compared with those with HbSC ($N = 6$; 28.6%) and HbSβ+ ($N = 2$; 66.7%) ($p < 0.001$). Folic acid supplementation was also more prevalent in the HbSS group ($N = 145$; 92.9%) ($p = 0.006$). Patients with HbSS reported a higher median number of blood transfusions in the past year (0–2) compared with patients with HbSC (0) and HbSβ+ (1) ($p = 0.008$). Iron chelation therapy was similar across all groups. (Table 1)

Table 1
Baseline characteristics of the study population classified by phenotype of SCD

Hemoglobin phenotype	SS N = 156	SC N = 21	SB+ N = 3	p
Demographic characteristic				
Male Sex, n (%)	55 (35.2)	8 (38.1)	2 (66.6)	0.522
Panama City, n (%)	109 (69.8)	18 (85.7)	1 (33.3)	0.112
Age, y, median (IQR)	28 (22–40)	26 (18–46)	20 (18–22.5)	0.273
Mestizo Race, n (%)	63 (52.0)	11 (73.3)	1 (33.3)	0.228
Hematological parameters				
Hemoglobin, g/dL, median (IQR)	7.8 (7.0–8.9)	11.2 (11.0–12.2)	12.2 (12.2–12.6)	< 0.001
Hematocrit, %, median (IQR)	22.6 (19.9–25.4)	30.7 (24.2–31.9)	35.5 (34.7–35.8)	< 0.001
MCV, fL, median (IQR)	90.0 (83.7–96.2)	83.0 (75.0–88.0)	102.0 (98.5–103.5)	< 0.001
Reticulocytes, %, median (IQR)	11.8 (8.4–17.0)	4.9 (4.3–8.0)	6.5 (6.1–6.9)	0.003
Leukocytes, ×10 ⁹ /L, median (IQR)	10.4 (8.5–13.1)	10.3 (7.8–12.3)	13.3 (12.2–13.9)	0.346
Platelets, ×10 ⁹ /L, median (IQR)	410 (311–505)	323 (182–481)	430 (414–440)	0.129
Hemolysis and biochemical markers				
Total bilirubin, mg/dL, median (IQR)	3.0 (2.1–4.8)	2.1 (1.7–2.8)	1.1 (1.0–1.2)	0.007
LDH, U/L, median (IQR)	695 (421–911)	422 (230–455)	208 (196–217)	< 0.001
Ferritin, ng/mL, median (IQR)	210 (96–444)	555 (448–1000)	617 (608–617)	0.40
Creatinine, mg/dL, median (IQR)	0.51 (0.40–0.66)	0.53 (0.40–0.70)	0.71 (0.65–0.71)	0.272
eGFR, mL/min/1.73m ² , median (IQR)	152 (128–169)	149 (125–164)	153 (145–155)	0.895
Treatment variables				
Hydroxycarbamide use, n (%)	118 (75.6)	6 (28.6%)	2 (66.7)	< 0.001

Hemoglobin phenotype	SS	SC	SB+	p
	N = 156	N = 21	N = 3	
Demographic characteristic				
Folic acid supplementation, n (%)	145 (92.9)	15 (71.4)	3 (100)	0.006
Iron chelation therapy, n (%)	6 (3.8)	1 (4.7)	0 (0)	0.921
Clinical outcomes				
Transfusions in the last year, median (IQR)	0 (0–2)	0 (0–0)	1 (1–1)	0.008
Pain crises in the last year, median (IQR)	1 (0–2)	0 (0–1)	1 (1–1)	0.206
Hospitalizations in the last year, median (IQR)	0 (0–1)	0 (0–0)	0 (0–0.5)	0.239
Acute chest syndrome, n (%)	14 (9)	0 (0)	0 (0)	0.311
Stroke, n (%)	12 (7.6)	0 (0)	0 (0)	0.372
Leg ulcer, n (%)	17 (11)	0 (0)	0 (0)	0.236
Avascular necrosis, n (%)	22 (14.1)	3 (14.3)	0 (0)	0.782
Cholecystectomy, n (%)	77 (49.5)	5 (23.8)	1 (33.3)	0.80
Opioid use, n (%)	46 (29.5)	5 (23.8)	0 (0)	0.472

eGFR, Estimated Glomerular Filtration Rate; IQR, interquartile range; n, number; LDH, lactate dehydrogenase; y, year;

Clinical outcomes

Regarding clinical outcomes, no statistically significant differences were observed in the prevalence of SCD-related complications, including pain crises, hospitalizations in the past year, acute chest syndrome, stroke, leg ulcers, and avascular necrosis. Cholecystectomy and opioid use also showed no significant differences between the phenotypes.

Association between the degree of anemia and SCD complications

In the general population, the lowest hemoglobin quartile (most severe anemia) was associated with a lower risk of developing avascular necrosis (OR 0.12; 95% CI, 0.03–0.62; $p = 0.011$). Similarly, in the HbSS phenotype, the lowest hemoglobin quartile was associated with a lower risk of avascular necrosis (OR 0.14; 95% CI, 0.03–0.72; $p = 0.019$). Adjusted for age, sex, and hydroxyurea use. No significant

associations were observed between hemoglobin levels and stroke (OR 1.27; $p = 0.787$), leg ulcers (OR 2.64; $p = 0.100$), or acute chest syndrome (OR 0.96; $p = 0.954$) in either the overall population or the HbSS subgroup (Table 2) These associations in the HbSS subgroup are illustrated in Fig. 3, which presents adjusted odds ratios for the relationship between low hemoglobin and clinical complications.

Table 2

Associations between SCD-related vascular complications and hemoglobin (quartile 1 vs quartiles 2 to 4 of hemoglobin) in the overall sample and SS phenotype: multivariate analysis

Complications	N event / N total	Quartile 1 (%)	Quartiles 2 to 4 (%)	Adjusted OR	95% CI	p*
Overall population (n = 180)						
Stroke, lifetime	12 / 180	16.7	7.5	1.27	0.23–7.00	0.787
Leg ulcer, lifetime	17 / 180	58.8	22.1	2.64	0.83–8.36	0.100
Avascular necrosis, lifetime	25 / 180	8.0	17.2	0.12	0.03–0.62	0.011
Acute chest syndrome, lifetime	14 / 180	21.4	25.9	0.96	0.22–4.18	0.954
SS phenotype (n = 156)						
Stroke, lifetime	12 / 156	16.7	9.1	1.27	0.23–7.00	0.787
Leg ulcer, lifetime	17 / 156	58.8	25.9	2.64	0.83–8.36	0.100
Avascular necrosis, lifetime	22 / 156	9.1	16.7	0.14	0.03–0.72	0.019
Acute chest syndrome, lifetime	14 / 156	21.4	30.3	0.96	0.22–4.18	0.954

CI, confidence interval; OR, Odds Ratio *Adjustment for Age, Sex and Hydroxyurea use

Forest plot of adjusted odds ratios for the association between low hemoglobin (Q1 vs Q2–Q4) and clinical complications in SS patients. Models were adjusted for age, sex, and hydroxyurea use. CI, confidence interval; OR, Odds Ratio.

Association between elevated LDH and SCD complications

In analyses adjusted for age and sex, elevated LDH levels (quartile 4 vs quartiles 1–3) were associated with an increased risk of acute chest syndrome in the overall cohort (OR 1.37; 95% CI, 0.39–4.78; $p = 0.033$) Higher LDH levels were also associated with avascular necrosis in the HbSS subgroup (OR 2.68; 95% CI, 1.03–7.01; $p = 0.044$), but not in the overall population (Table 3). No significant associations

were observed between LDH levels and stroke or leg ulcers in either the overall cohort or the HbSS subgroup (all $p > 0.05$) (Fig. 4)

Table 3
Associations between SCD-related vascular complications and LDH (quartile 1–3 vs quartiles 4 of LDH) in the overall sample and SS phenotype: multivariate analysis

Complications	N event / N total	Quartile 1–3 (%)	Quartiles 4 (%)	Adjusted OR	95% CI	p*
Overall population (n = 180)						
Stroke, lifetime	12/180	7.4	4.4	0.84	0.17–4.29	0.621
Leg ulcer, lifetime	17/180	8.1	13.3	1.38	0.46–4.11	0.837
Avascular necrosis, lifetime	25/180	10.3	24.4	2.64	1.08–6.45	0.567
Acute chest syndrome, lifetime	14/180	7.4	8.8	1.37	0.39–4.78	0.033
SS phenotype (n = 156)						
Stroke, lifetime	12/156	7.4	4.4	0.83	0.16–4.40	0.826
Leg ulcer, lifetime	17/156	9.6	14.2	1.13	0.37–3.46	0.825
Avascular necrosis, lifetime	22/156	10.5	23.8	2.68	1.03–7.01	0.044
Acute chest syndrome, lifetime	14/156	8.7	9.5	1.25	0.35–4.45	0.734

CI, confidence interval; OR, Odds Ratio; HbSS, Hemoglobin SS; HbSC, Sickle Hemoglobin C Disease; HBSB+, Sickle Beta-Plus Thalassemia. *Adjustment for Age and Sex. $p > 0.05$ was considered significant.

Forest plot of adjusted odds ratios for the association between elevated LDH (Q4 vs Q1–3) and clinical complications in SS patients. Models were adjusted for age and sex. CI, confidence interval; OR, Odds Ratio; LDH, lactate dehydrogenase.

DISCUSSION

This cohort of adult Panamanian patients with sickle cell disease (SCD) represents the first study conducted at Hospital Santo Tomás in Panama City. We found that anemia severity and hemolysis exert distinct effects on vascular complications. Lower hemoglobin levels (quartile 1) were associated with a reduced risk of avascular necrosis in both the overall cohort and the HbSS phenotype, whereas higher

LDH levels (quartiles 2–4) were associated with an increased risk of acute chest syndrome in the overall population and with avascular necrosis among HbSS patients.

These findings align in part with the current paradigm describing SCD as comprising overlapping but biologically distinct sub phenotypes: a hemolysis-driven vasculopathy phenotype and a viscosity-driven vaso-occlusive phenotype (13, 19). The association between relatively higher hemoglobin levels and increased risk of avascular necrosis supports prior evidence linking vaso-occlusive complications to increased blood viscosity rather than anemia severity. Mechanistically, higher hemoglobin concentrations increase blood viscosity, erythrocyte aggregation, and microvascular flow resistance, promoting vaso-occlusion and ischemia–reperfusion injury (20).

In contrast, our findings regarding hemolysis diverge from prior reports. Previous studies, including Kato et al., have suggested that the hyper hemolytic phenotype is associated with a lower risk of avascular necrosis (13), and a retrospective cohort reported an inverse association between LDH levels and femoral head avascular necrosis ($p = 0.006$) (21). However, we observed that higher LDH levels were associated with increased risk of avascular necrosis, particularly in HbSS patients. This finding suggests that hemolysis may contribute to microvascular injury in bone through mechanisms of endothelial dysfunction, nitric oxide depletion, oxidative stress, and inflammation (13).

Taken together, our results suggest that avascular necrosis may lie at the intersection of hemolysis- and viscosity-driven pathways, rather than being exclusively viscosity-mediated. This integrated model is supported by growing evidence that hemolysis biomarkers reflect overall disease severity and organ damage (4).

We also observed a significant association between elevated LDH and acute chest syndrome, supporting a role for hemolysis in acute organ injury. Experimental and clinical data indicate that heme released during hemolysis acts as a damage-associated molecular pattern (DAMP), activating innate immune pathways and promoting endothelial injury in the lungs (23). These mechanisms, along with nitric oxide dysregulation and oxidative stress, may contribute to the development of acute chest syndrome (24).

In contrast, we did not observe significant associations between LDH and chronic complications such as stroke or leg ulcers. While prior studies have linked hemolysis to vasculopathy complications, including leg ulcers and stroke (13, 22), and similar findings have been reported in African cohorts (16), these outcomes are likely multifactorial and may reflect cumulative vascular injury over time, which may not be fully captured in cross-sectional analyses (25–27). Notably, some studies have also reported no association between hemolysis and cerebrovascular disease (16), consistent with our findings.

This study has several limitations. The relatively small sample size, particularly for non-HbSS genotypes, limited statistical power and subgroup analyses. The genotype distribution in our cohort (86.7% HbSS, 11.7% HbSC, 1.7% HbS β +) differs from that reported in African (15, 16) and Middle Eastern populations (17, 18), where HbSC and HbS β + are more prevalent. This likely reflects selection bias inherent to a single tertiary referral center, with preferential inclusion of patients with more severe disease. The

retrospective cross-sectional design precludes causal inference and is subject to information and reporting bias. Additionally, residual confounding is possible, as key modifiers such as fetal hemoglobin levels and treatment adherence were not available. Finally, LDH is an imperfect marker of hemolysis and may reflect tissue injury beyond erythrocyte destruction (20).

Despite these limitations, our findings support a multidimensional model of SCD pathophysiology in which hemolysis, viscosity, inflammation, and endothelial dysfunction interact dynamically rather than acting as independent processes. This integrated perspective may have important clinical implications, particularly for risk stratification and phenotype-driven therapeutic strategies.

Given the single-center design, external validity may be limited; however, the predominance of HbSS and the observed clinical profile are broadly consistent with cohorts from other low- and middle-income settings (15–18). Prospective, multicenter studies are needed to validate these findings and to better define the role of hemolysis biomarkers in predicting vascular complications across diverse populations.

Declarations

Authorship Contribution(s)

Niko Díaz was responsible for designing the research study, analyzed the data, data collection and wrote the paper.

María Mantilla, Fernando Carrillo and Lorena Ordoñez. were responsible for the research, data collection and wrote the paper.

Germán Espino: performed the research and designed the research study and revised critically for important intellectual content.

All authors reviewed and approved the manuscript.

Acknowledgements: None.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding information: This research did not receive any funding from agencies in the public, commercial, or not-for-profit sectors.

Data Availability: Data is available upon request.

References

1. Rees DC, Williams TN, Gladwin MT (2010) Sickle-cell disease. *Lancet* 376(9757):2018–2031. 10.1016/S0140-6736(10)61029-X

2. Piel FB, Steinberg MH, Rees DC (2017) Sickle Cell Disease. Longo DL, editor. *N Engl J Med*. ;376(16):1561–73. 10.1056/NEJMra1510865
3. Kavanagh PL, Fasipe TA, Wun T (2022) Sickle Cell Disease: A Review. *JAMA* 328(1):57. 10.1001/jama.2022.10233
4. Hamed NF, Alatawi YDA, AlKabbani DMZ, Prevalence (2024 Jul) Risk Factors, and Complications of Sickle Cell Disease in Saudi Arabia: A Systematic Review. *Cureus* 24. 10.7759/cureus.65263
5. Thomson AM, McHugh TA, Oron AP, Teply C, Lonberg N, Vilchis Tella V et al (2023) Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Haematol* 10(8):e585–e599. 10.1016/S2352-3026(23)00118-7
6. Colombatti R, Jastaniah W, Makani J, Andemariam B (2026) Sickle cell disease. *Lancet* 407(10533):1095–1111. 10.1016/S0140-6736(25)02278-0
7. Mikobi TM, Lukusa Tshilobo P, Aloni MN, Mvumbi Lelo G, Akilimali PZ, Muyembe-Tamfum JJ et al (2015) Correlation between the Lactate Dehydrogenase Levels with Laboratory Variables in the Clinical Severity of Sickle Cell Anemia in Congolese Patients. Connes P, editor. *PLOS ONE*. ;10(5):e0123568. 10.1371/journal.pone.0123568
8. Feugray G, Dumesnil C, Grall M, Benhamou Y, Girot H, Fetting J et al (2023) Lactate dehydrogenase and hemolysis index to predict vaso-occlusive crisis in sickle cell disease. *Sci Rep* 13(1):21198. 10.1038/s41598-023-48324-w
9. Kato GJ, McGowan V, Machado RF, Little JA, Taylor J, Morris CR et al (2006) Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. *Blood* 107(6):2279–2285. 10.1182/blood-2005-06-2373
10. Connes P, Lamarre Y, Waltz X, Ballas SK, Lemonne N, Etienne-Julan M et al (2014) Haemolysis and abnormal haemorheology in sickle cell anaemia. *Br J Haematol* 165(4):564–572. 10.1111/bjh.12786
11. Olle H, Añez A, PREVALENCE OF SICKLE CELL DISEASE IN PANAMA: (2026) A SYSTEMATIC LITERATURE REVIEW (2020–2025). *Gente Clave* 10(1):96–106. 10.65050/rgc.v10n1a7
12. Ágrede F, Arcia E, Jované S, Pino E, Tufiño E, JUNIO. FRECUENCIA DE PORTADORES DEL ALELO S EN LA (2004) POBLACIÓN DE 15-49 AÑOS DE PORTOBELO. PANAMÁ
13. Kato GJ, Gladwin MT, Steinberg MH (2007) Deconstructing sickle cell disease: Reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Rev* 21(1):37–47. 10.1016/j.blre.2006.07.001
14. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y et al (2021) New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *N Engl J Med* 385(19):1737–1749. 10.1056/NEJMoa2102953
15. Amuzu EX, Urio F, Dogbe EE, Ponsian P, Abubakar SY, Okeke C et al (2025) Clinical manifestations of sickle cell disease in Africa and its association with foetal haemoglobin parameters. *Commun Med*

5(1):238. 10.1038/s43856-025-00954-z

16. Dubert M, Elion J, Tolo A, Diallo DA, Diop S, Diagne I et al (2017) Degree of anemia, indirect markers of hemolysis, and vascular complications of sickle cell disease in Africa. *Blood* 130(20):2215–2223. 10.1182/blood-2016-12-755777
17. Ata F, Rahhal A, Malkawi L, Iqbal P, Khamees I, Alhiyari M et al (2023) Genotypic and Phenotypic Composition of Sickle Cell Disease in the Arab Population - A Systematic Review. *Pharmacogenomics Pers Med* 16:133–144. 10.2147/PGPM.S391394
18. El-Hazmi MAF, Al-Hazmi AM, Warsy AS (2011) Sickle cell disease in Middle East Arab countries. *Indian J Med Res* 134(5):597–610. 10.4103/0971-5916.90984 PubMed PMID: 22199098; PubMed Central PMCID: PMC3249957
19. Stankovic Stojanovic K, Lionnet F (2016) Lactate dehydrogenase in sickle cell disease. *Clin Chim Acta* 458:99–102. 10.1016/j.cca.2016.04.035
20. Kato GJ, Steinberg MH, Gladwin MT (2017) Intravascular hemolysis and the pathophysiology of sickle cell disease. *J Clin Invest* 127(3):750–760. 10.1172/JCI89741
21. Ouederni M, Rouag H, Ben Fraj I, Rekaya S, Kouki R, Lamouchi T et al (2023) Incidence and risk factors for osteonecrosis of the femoral head in five hundred and ten sickle cell disease paediatric patients. *Int Orthop* 47(12):2941–2952. 10.1007/s00264-023-05886-8
22. Antwi-Boasiako C, Andemariam B, Colombatti R, Asare EV, Strunk C, Piccone CM et al (2020) A study of the geographic distribution and associated risk factors of leg ulcers within an international cohort of sickle cell disease patients: the CASiRe group analysis. *Ann Hematol* 99(9):2073–2079. 10.1007/s00277-020-04057-8
23. Ghosh S, Adisa OA, Chappa P, Tan F, Jackson KA, Archer DR et al (2013) Extracellular hemin crisis triggers acute chest syndrome in sickle mice. *J Clin Invest* 123(11):4809–4820. 10.1172/JCI64578
24. Yildirim N, Unal S, Yalcinkaya A, Karahan F, Oztas Y (2022) Evaluation of the relationship between intravascular hemolysis and clinical manifestations in sickle cell disease: decreased hemopexin during vaso-occlusive crises and increased inflammation in acute chest syndrome. *Ann Hematol* 101(1):35–41. 10.1007/s00277-021-04667-w
25. Taylor JG, Nolan VG, Mendelsohn L, Kato GJ, Gladwin MT, Steinberg MH (2008) Chronic Hyper-Hemolysis in Sickle Cell Anemia: Association of Vascular Complications and Mortality with Less Frequent Vasoocclusive Pain. Reitsma PH, editor. *PLoS ONE*. ;3(5):e2095. 10.1371/journal.pone.0002095
26. Idris IM, Botchwey EA, Hyacinth HI (2022) Sickle cell disease as an accelerated aging syndrome. *Exp Biol Med* 247(4):368–374. 10.1177/15353702211068522
27. Department of Basic Sciences, Faculty of Applied Medical Sciences, University A-B, Arabia A-B, Alzahrani HA (2025) The Impact of Aging on Organ Systems in Sickle Cell Disease: a Comparative Review of Physiological Adaptation and Dysfunction. *Cell Physiol Biochem*. ;59(6):930–9. 10.33594/000000839

Figures

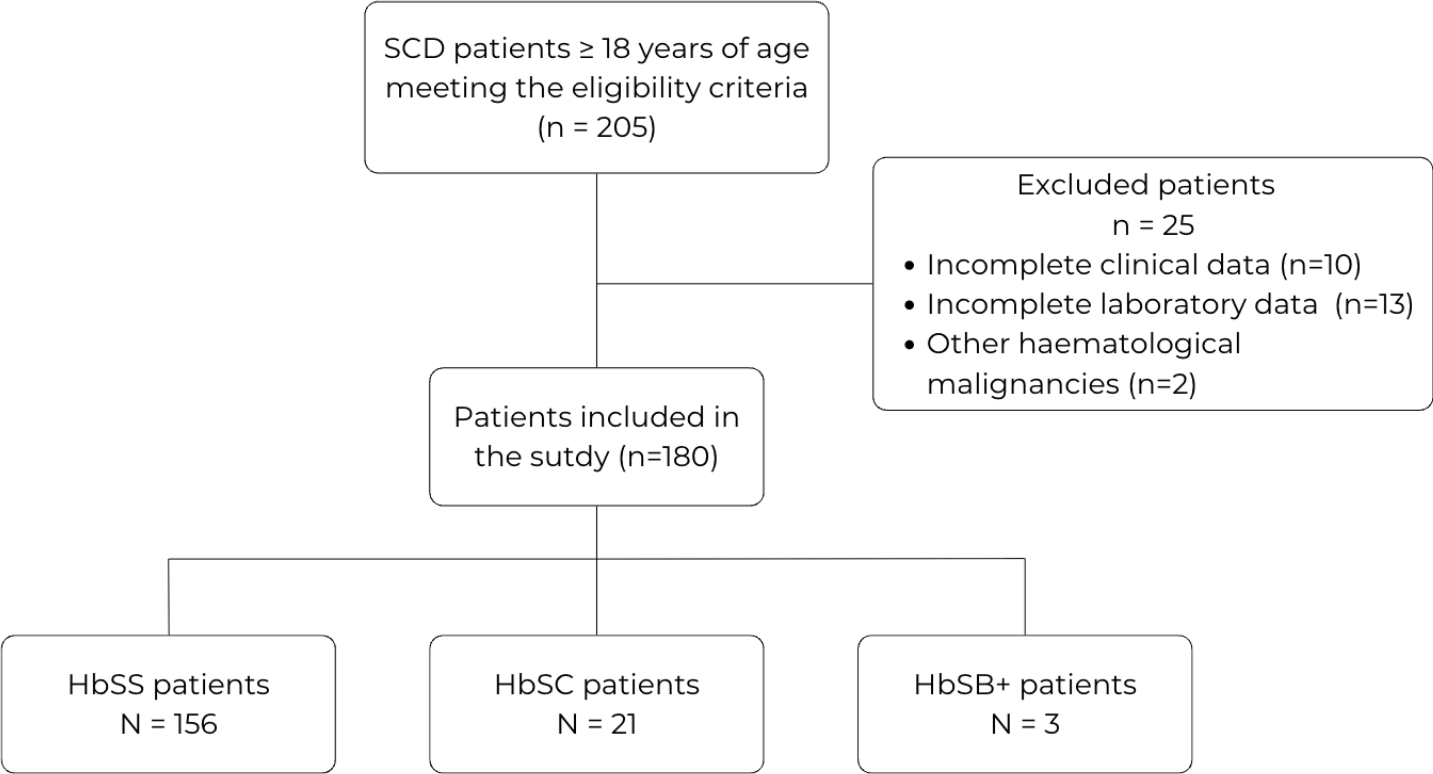


Figure 1

Flow diagram of patient selection and genotype distribution in the study cohort

SCD, Sickle cell disease; HbSS, Hemoglobin SS; HbSC, Sickle Hemoglobin C Disease; HBSB+, Sickle Beta-Plus Thalassemia.

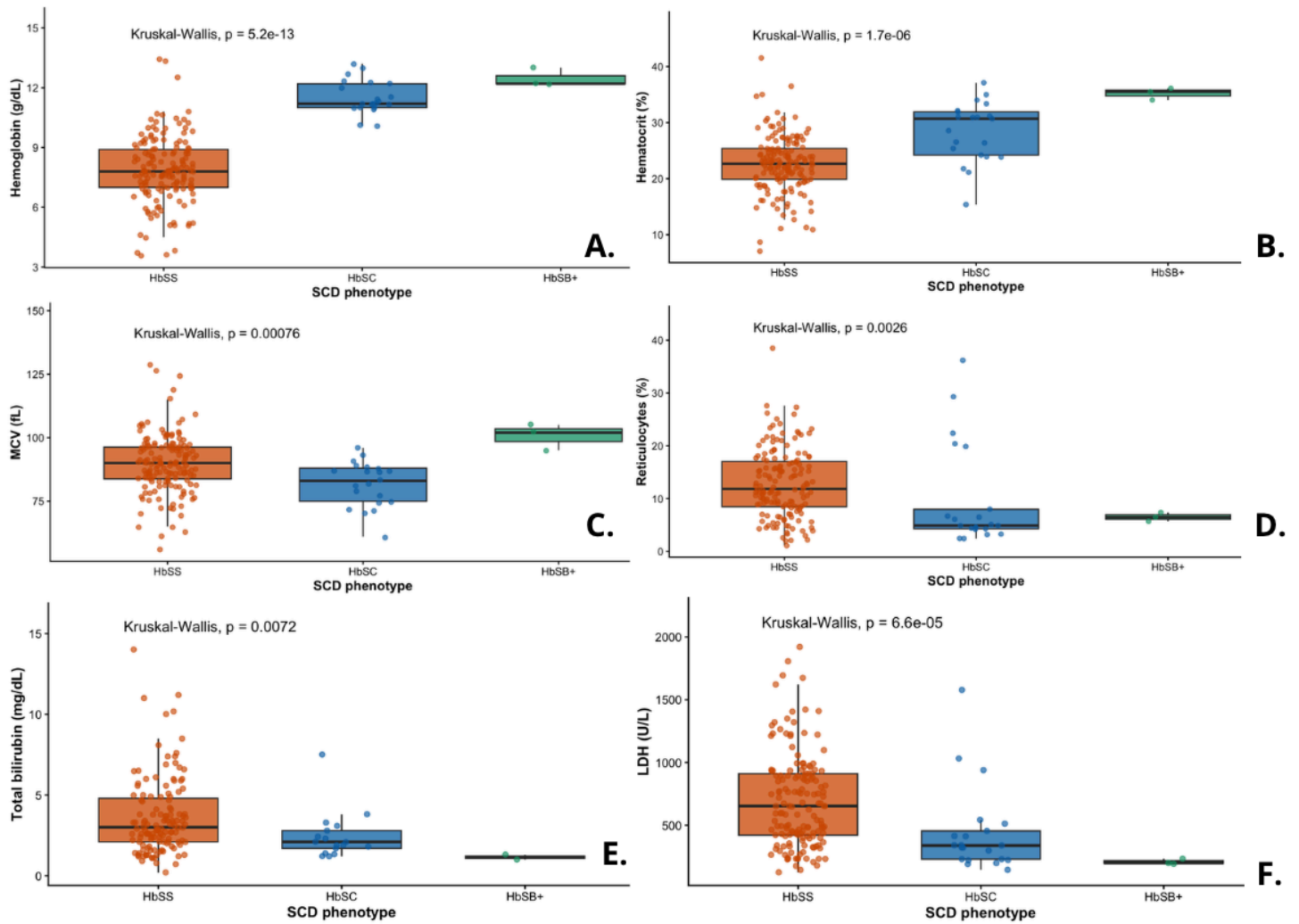


Figure 2

Haematological and haemolysis-related parameters according to sickle cell disease phenotype

Panels show haemoglobin (A), hematocrit (B), mean corpuscular volume (MCV) (C), reticulocyte percentage (D), total bilirubin (E), and lactate dehydrogenase (LDH) (F) according to phenotype (HbSS, HbSC, and HbSB+). Data are presented as boxplots with individual observations. Comparisons between groups were performed using the Kruskal-Wallis test.

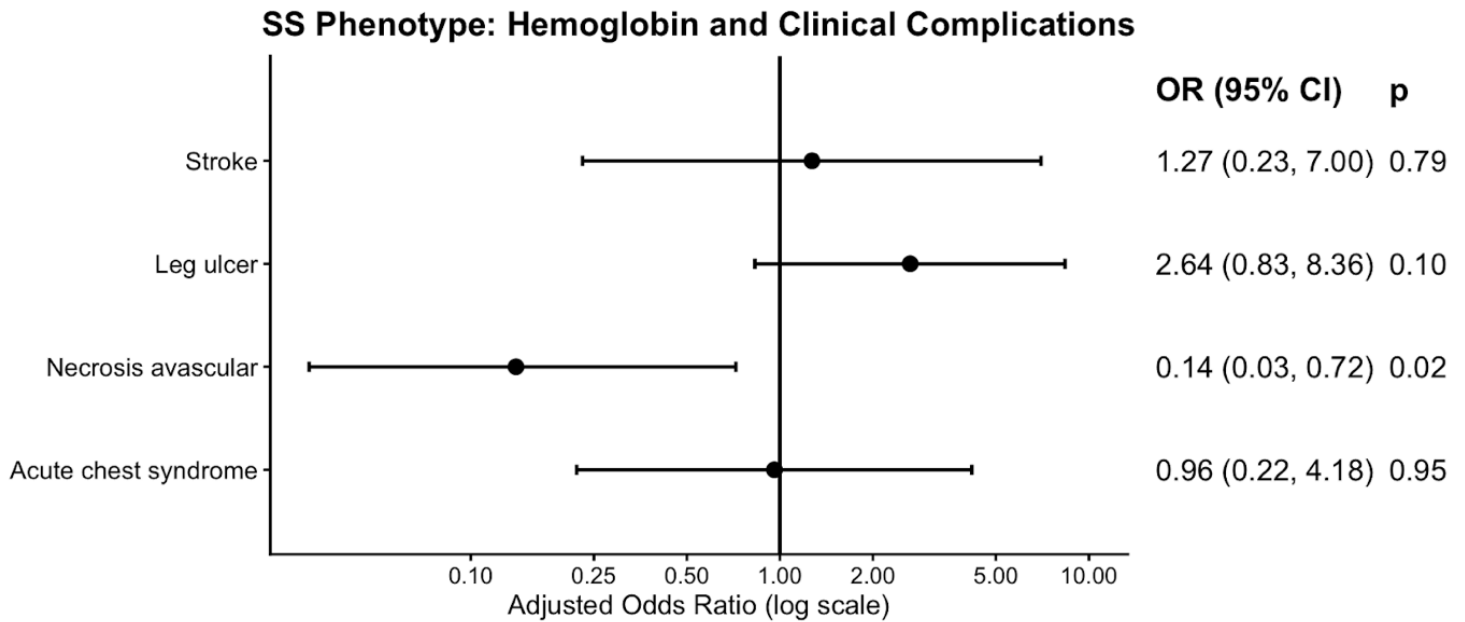


Figure 3

Association Between Low Hemoglobin and Clinical Complications in Adults With Sickle Cell Disease (SS Phenotype)

Forest plot of adjusted odds ratios for the association between low hemoglobin (Q1 vs Q2–Q4) and clinical complications in SS patients. Models were adjusted for age, sex, and hydroxyurea use. CI, confidence interval; OR, Odds Ratio.

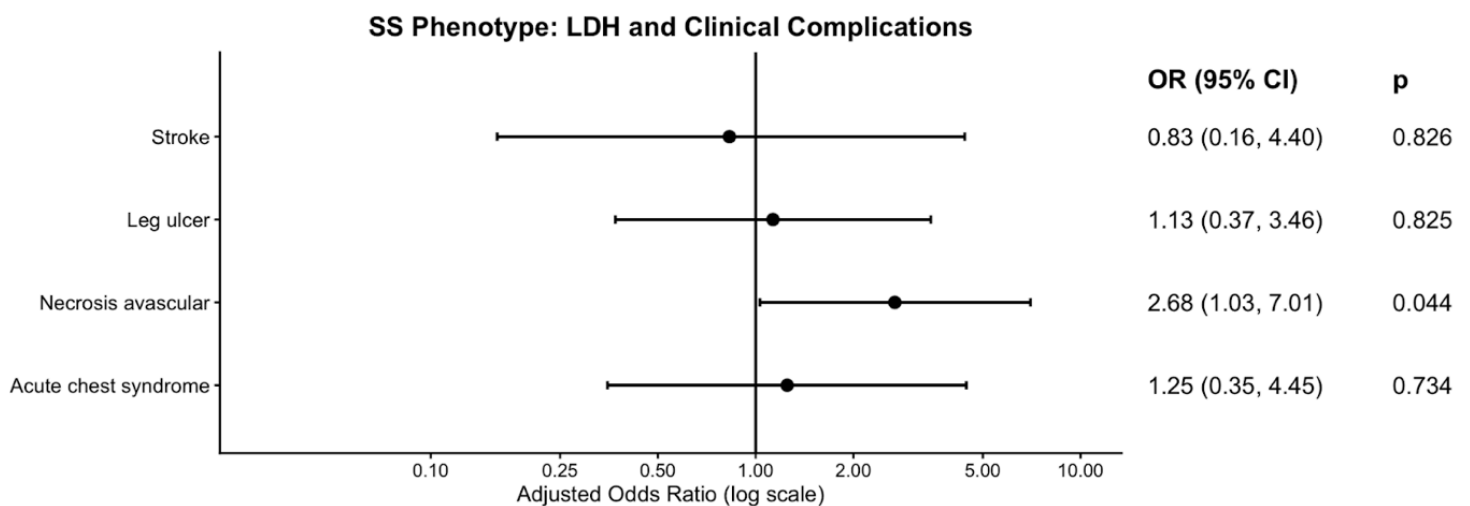


Figure 4

Association Between Elevated Lactate Dehydrogenase and Clinical Complications in Adults With Sickle Cell Disease (SS Phenotype)

Forest plot of adjusted odds ratios for the association between elevated LDH (Q4 vs Q1–3) and clinical complications in SS patients. Models were adjusted for age and sex. CI, confidence interval; OR, Odds Ratio; LDH, lactate dehydrogenase.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [COIALLAUTHORS.pdf](#)